

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
28 October 2004 (28.10.2004)

PCT

(10) International Publication Number  
**WO 2004/091632 A1**

(51) International Patent Classification: A61K 31/58,  
31/50, 31/49, 31/40, 31/41, A61P 9/06, 9/04

(21) International Application Number:  
PCT/HU2004/000036

(22) International Filing Date: 14 April 2004 (14.04.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
P 0300985 15 April 2003 (15.04.2003) HU

(71) Applicant (for all designated States except US): SYN-  
OSENS KUTATÓ ÉS FEJLESZTŐ KFT. (HU/HU);  
Szent István Krt. 18., H-1137 Budapest (HU).

(72) Inventor; and

(75) Inventor/Applicant (for US only): EGRÍ, János  
(HU/HU); Dereglye u. 2., H-1036 Budapest (HU).

(74) Agent: ADVOPATENT; Office of Patent and Trademark  
Attorneys, P.O. Box 11, H-1251 Budapest (HU).

(81) Designated States (unless otherwise indicated, for every  
kind of national protection available): AR, AG, AL, AM,

AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,  
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,  
GB, GD, GE, GH, GM, GR, GU, HT, IL, IN, IS, JP, KE,  
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,  
MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG,  
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,  
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,  
ZW.

(84) Designated States (unless otherwise indicated, for every  
kind of regional protection available): ARIPO (BW, GH,  
GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),  
Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Euro-  
pean (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR,  
GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK,  
TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,  
ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the  
claims and to be republished in the event of receipt of  
amendments

For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.

(54) Title: A PHARMACEUTICAL COMPOSITION CONTAINING AN ACTIVE AGENT HAVING THE EFFECT OF DIGI-  
TALIS AND A COMB PHOSPHODIESTERASE INHIBITOR

(57) Abstract: The invention refers to a cardiostonic pharmaceutical composition having enhanced therapeutical width. The phar-  
macological composition of the invention comprises (a) an active ingredient having the effect of digitalis and (b) a cAMP phosphodi-  
esterase inhibitor and one or more conventional carrier(s).

WO 2004/091632 A1

10/553446

JC09 Rec'd PCT/PTO 14 OCT 2005

PCT/HU2004/000036

Amended page

1/a

5 Clement et al. described a study in which the effect of a combined cicletanine and digoxin therapy on plasma digoxin level was investigated [Clement, D.L. et al.: „Lack of Effect of Cicletanine on Plasma Digoxin Levels", Int. J. Clin. Pharm. Res., 8(1), 9-11 (1988)]. The study performed on six patients did not reveal any significant change in plasma digoxin concentration, however, stated that the combined treatment was well tolerated.

10 Bukoski et al. investigated the vascular effect of cicletanine [Bukoski, R.D. et al.: „Vascular actions of cicletanine", Archives des Maladies du Coeur et des Vaisseaux, 82(4), 45-50 (1989)]. Cicletanine induced relaxation of vessels, and the relaxation was not inhibited in case of vessels pretreated with ouabain, 15 moreover, at lower doses, a slight potentiation of the relaxation could be observed.

The literature data do not hint at any influence of phosphodiesterase inhibitors on the arrhythmogenic effect of digitalis glycosides.

PCT/HU2004/000036

Amended page

13

## Claims:

1. Use of a cGMP phosphodiesterase inhibitor for the preparation of a pharmaceutical composition to eliminate the emergence of arrhythmogenic side effects of a cardiotonic therapy with a digitalis glycoside or digitaloide.  
5
2. The use of Claim 1 in which the cGMP phosphodiesterase inhibitor is cicletanine, vinpocetine, sildenafil or zaprinast or, if chemically possible, a pharmaceutically suitable acid addition salt thereof.  
10
3. The use of Claim 2 in which the cGMP phosphodiesterase inhibitor is cicletanine or a pharmaceutically suitable acid addition salt thereof.
4. A method for reducing the dose of a digitalis glycoside or digitaloide required for cardiotonic therapy in which a patient  
15 being in need of a cardiotonic treatment with a digitalis glycoside or digitaloide is treated, in addition to the digitalis glycoside or digitaloide, also with a cGMP phosphodiesterase inhibitor.

# INTERNATIONAL SEARCH REPORT

Int. Application No  
PCT/HU2004/000036

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/58 A61K31/50 A61K31/49 A61K31/40 A61K31/41  
A61P9/06 A61P9/04

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, EMBASE, MEDLINE, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No. |
|------------|--|-----------------------|
| X          | CLEMENT, D. L. ET AL.: "Lack of Effect of Cicletanine on Plasma Digoxin Levels"<br>INTERNATIONAL JOURNAL OF CLINICAL PHARMACOLOGY RESEARCH,<br>vol. 8, no. 1, 1988, pages 9-11,<br>XP008033838<br>abstract | 1-4                   |
| X          | BUKOSKI, R. D. ET AL.: "Vascular actions of cicletanine"<br>ARCHIVES DES MALADIES DU COEUR ET DES VAISSEAUX,<br>vol. 82, no. 4, 1989, pages 45-50,<br>XP008033902<br>abstract                              | 1-4                   |

☐ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

### \* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the International filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the International filing date but later than the priority date claimed

"T" later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the International search

19 August 2004

Date of mailing of the international search report

31/08/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Beyss, E

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/HU2004/000036

### Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claim 8 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

#### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.